AMISOMETRADINE (ROLICTON) IN THE TREATMENT OF CONGESTIVE HEART FAILURE

BY

MARGARET M. PLATTS*

From the Department of Medicine, The University of Sheffield

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The oral diuretic amisometradine (rolicton) is an isomer of aminometradine (mictine) but is relatively free from toxic effects while maintaining a reasonable diuretic potency (Belle, 1957; Settel, 1957; Jose and Wood, 1958). The present study was designed to assess the usefulness of amisometradine in the treatment of patients with congestive heart failure and to compare the excretion of water and electrolytes produced by it with that elicited by mersalyl.

Material and Methods

Seventeen patients suffering from untreated congestive heart failure of moderate severity were treated with amisometradine. Patients whose condition made immediate therapy with diuretics imperative were excluded from the trial. Twelve of the patients were suffering from pulmonary heart failure, two from mitral stenosis, and one each from pernicious anæmia and ischæmic and hypertensive heart disease.

Each patient was weighed daily and received a diet containing a constant amount of sodium chloride (either 500 mg. or 2 g.) and fluid (1000 or 1200 ml.) each day. Twenty-four hour collections of urine were made from 16 patients throughout the study. One to six control days preceded the administration of a diuretic. Patients who had a spontaneous diuresis during this period were excluded from the investigation. Treatment with digitalis, antibiotics, and other non-diuretic drugs was given as required, but wherever possible this treatment was instituted at the beginning of the "control" period and was not altered until the trial of the diuretic had been completed.

In 16 patients the effects of amisometradine were compared with those of mersalyl. Since administration of any diuretic may change the patients' condition, amisometradine was given before mersalyl to nine patients and the mersalyl first to the other seven. Mersalyl was administered intramuscularly in doses of 2 ml. and was not preceded by ammonium chloride. Amisometradine was given orally in amounts ranging from 400 mg. every 12 hours to 800 mg. every 8 hours for two to sixteen days.

The sodium, potassium, and chloride content of each specimen of urine were measured and in most patients the concentrations of these electrolytes in the plasma were estimated before and after treatment with amisometradine. Sodium and potassium concentrations were measured by flame photometry and the chloride concentration by potentiometric titration with silver nitrate (Sanderson, 1952).

In addition to these acute observations 10 out-patients who had recovered from attacks of congestive cardiac failure were treated with amisometradine.

Results

Therapeutic Effect in Congestive Heart Failure. The clinical response of the patients with congestive heart failure to amisometradine was classified as "good", if the average weight loss during

* J. G. Graves Research Fellow.

treatment was 0·5 kg. or more per day, and as "failure" if no weight loss occurred. Patients who lost weight at a rate of less than 0·5 kg. per day were considered to have had a "fair" result. Judged on this basis 12 of the 17 patients had a good or fair response (Table I). Six patients became free from œdema after 5 to 9 days' treatment. Administration of amisometradine was stopped in two other patients who were responding well but had not become free from œdema, so that the comparison with mersalyl could be made.

Amisometradine usually produced the greatest increase in urine volume on the second or third day of treatment. In most of the patients in whom a good or fair response was obtained the diuresis persisted during the 24 hour period after the last treatment day (Fig. 1).

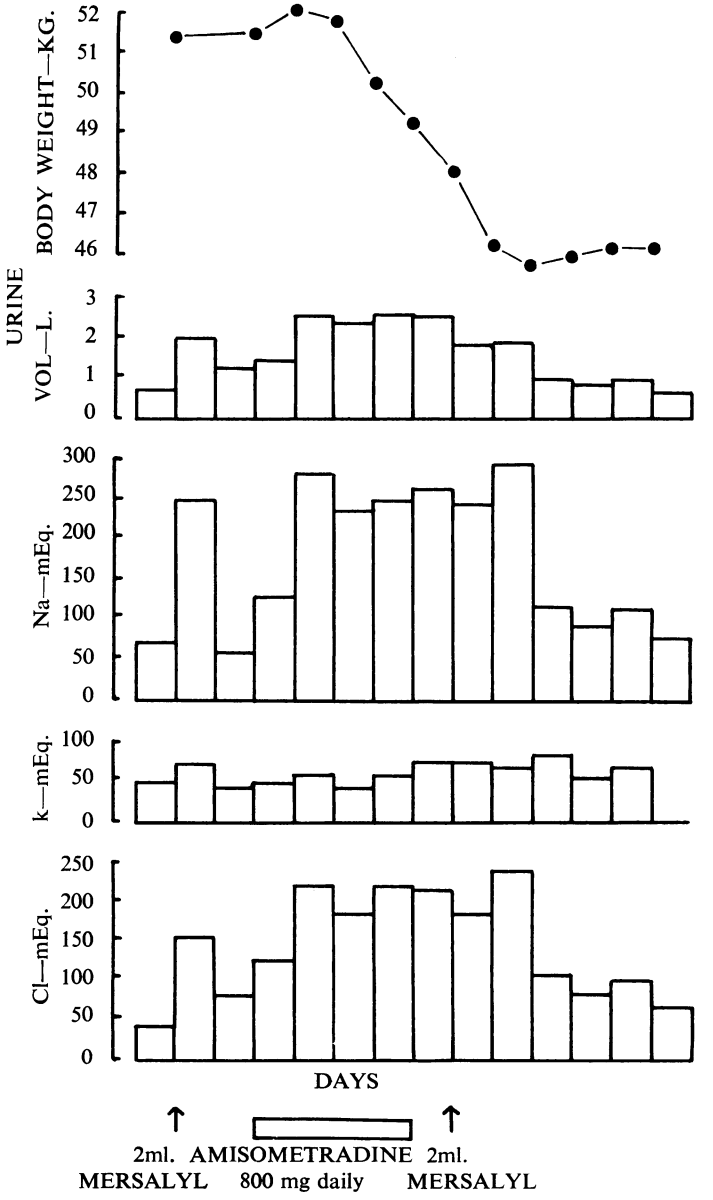

FIG. 1.—Changes in weight and electrolyte excretion occurring in a patient who responded well to amisometradine.

The number of patients treated was too small to assess the effects of different doses accurately but 800 mg. twice daily seemed to be the optimum dose (Table I).

TABLE I

CLINICAL RESPONSE OF PATIENTS WITH CONGESTIVE CARDIAC FAILURE TO DIFFERENT DOSES OF AMISOMETRADINE

No. of patients	Dose	Dose that gave better response	Results of treatment		
			Good	Fair	Failure
5	400 mg. b.d.	—	1	3	1
4	400 mg. to 800 mg. b.d.	800 mg. b.d. in 3 patients	2	1	1
6	800 mg. b.d.	—	3	1	2
2	800 mg. b.d. to 800 t.d.s.	800 mg. b.d. in 2 patients	0	1	1
		Total	6	6	5

Comparison of Diuretic Effects of Amisometradine and Mersalyl (Fig. 2). The urine volume and electrolyte excretion during treatment with amisometradine or mersalyl have been expressed as the

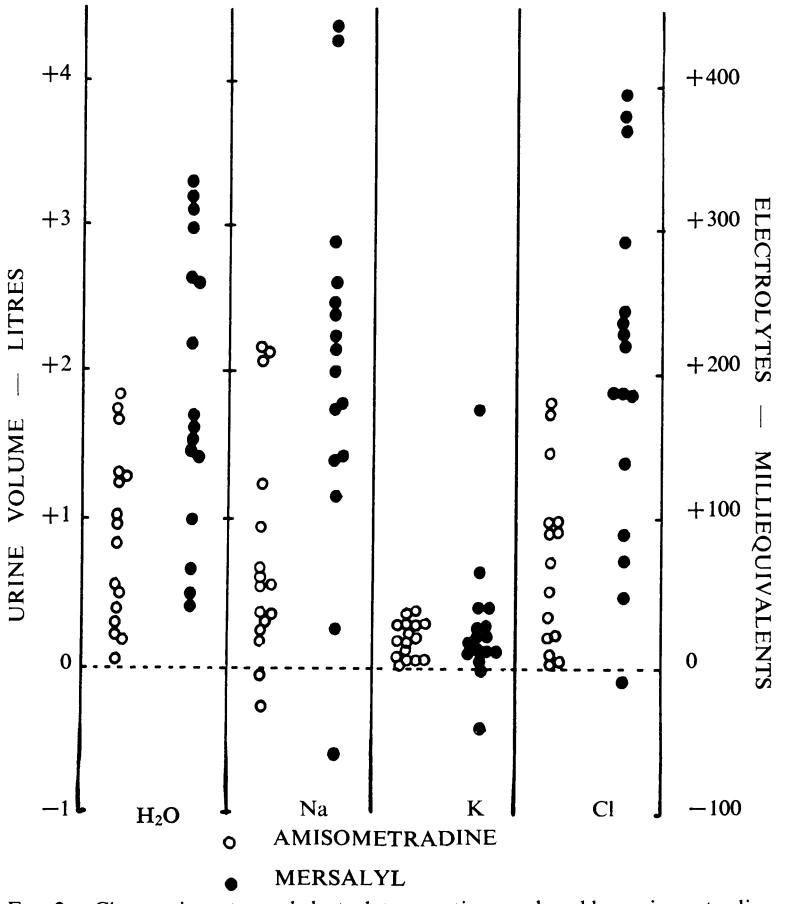

FIG. 2.—Changes in water and electrolyte excretion produced by amisometradine and mersalyl respectively in 16 patients with congestive heart failure. Negative values denote fluid or electrolyte retention when compared with the average values during the control period. In each patient the largest 24 hr. volume of urine ecreted during treatment with amisometradine is compared with the larger produced after a single dose of mersalyl.

change in excretion of each constituent in 24 hours compared with the average value during the control period (Fig. 2). In 5 of the 16 patients the greatest 24-hour urine volume and sodium excretion during treatment with amisometradine exceeded those produced by mersalyl. Four of these were patients to whom mersalyl was given after amisometradine. In all the others the maximal daily urine volume and sodium loss following mersalyl were greater than on any single day after amisometradine. In 5 out of the 6 who received mersalyl both before and after amisometradine, mersalyl produced a larger diuresis after amisometradine than it did before. In two patients a partial resistance to mersalyl was abolished after a short course of amisometradine (Fig. 3).

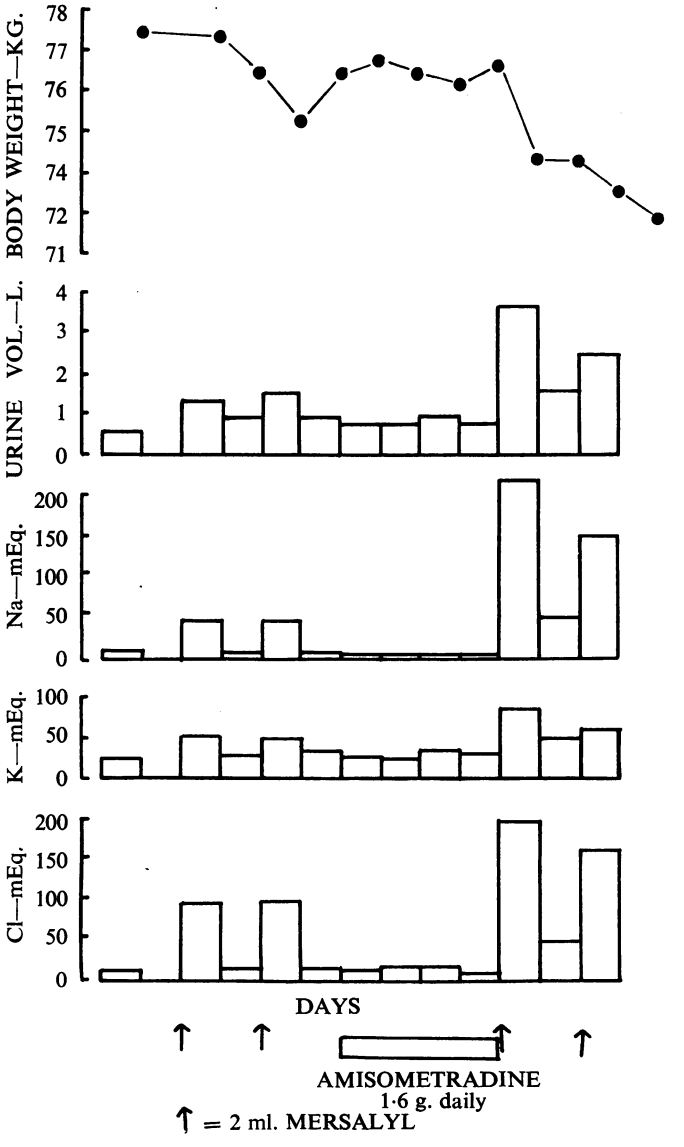

FIG. 3.—Patient initially partially resistant to mersalyl in whom a short course of amisometradine was followed by an increased response to mersalyl.

Amisometradine usually caused a diuresis of sodium and chloride in approximately equimolecular concentrations. However, in the 4 patients who lost more than 100 mEq. of sodium daily in excess of the control excretion, chloride excretion was about 20 per cent less than that of sodium.

Effect of Amisometradine on Ambulant Patients with Heart Disease. Ten out-patients who had recovered from attacks of congestive heart failure received 400 to 800 mg. of amisometradine twice daily for 5 days a week over periods of three weeks to fifteen months. In two the number of mersalyl injections on which they had been maintained was reduced from two to one per week when treatment with amisometradine was begun. One of these patients gained 2·3 kg. in weight during the ensuing month and treatment with amisometradine was abandoned. The other has remained well for ten weeks. Two patients who had been free from œdema for a year on one injection of mersalyl a week were given 800 mg. of rolicton twice daily in place of the mersalyl. One of these has remained well for fifteen months but the other became œdematous again in five weeks.

Of the other 6 patients who were discharged from hospital on amisometradine 3 were receiving mersalyl as well and 2 were intolerant of mercurial diuretics. Four of these six patients were re-admitted with recurrencies of congestive heart failure from one to five months later. All these patients had had more than one previous attack of cardiac failure.

Toxic Effects.—Out of a total of 23 patients 6 were nauseated while taking amisometradine. In one the nausea was relieved by withholding digitalis and in another vomiting occurred 48 hours after stopping amisometradine. A third developed nausea simultaneously with the onset of a further attack of heart failure. None of the patients vomited while receiving the drug.

No significant changes in the plasma sodium or chloride concentrations occurred in 13 patients treated with amisometradine for periods of from two days to four months. A reduction in plasma potassium concentration was observed in 8 of these 13 patients but in only two did this exceed 0·5 mEq/l. The lowest plasma potassium concentration recorded during treatment was 3·0 mEq/l. but no symptoms of potassium depletion occurred. No other toxic effects were encountered.

Discussion and Conclusions

Amisometradine is a useful oral diuretic, producing loss of weight in two-thirds of patients with moderately severe congestive cardiac failure. Belle (1958) obtained a satisfactory therapeutic response in 92 per cent of his ambulant patients with heart failure who were probably less severely ill than those in the present series.

The diuresis produced by amisometradine is sustained and though the daily urine flow may not be dramatic the cumulative effect over a period of several days may compare favourably with the intermittent diuresis produced by mersalyl given two or three times a week. Jose and Wood (1958) conclude that 2·4 g. of amisometradine given over 48 hours has approximately 40 per cent of the diuretic potency of 2 ml. of mersalyl measured over 24 hours. This measurement probably underestimates the relative efficacy of amisometradine given for longer periods since the maximum diuresis produced by this drug may not be attained for three or more days. On the other hand fluid retention frequently occurs during the second 24-hour period after administration of mersalyl.

A figure in Jose and Wood's paper confirms our finding that the diuresis often persists for 24 hours after withholding amisometradine. This suggests delayed excretion of the drug and it therefore seems wise that long-term treatment with the drug should not be continuous but that one or two days' rest should be given each week to prevent undue accumulation of the drug. Our impression that 800 mg. twice daily is the optimum dose in general for adults with congestive cardiac failure confirms the finding of Settel (1957), who obtained a greater diuresis with 1·5 to 2 g. daily than he did with 0·6 to 0·8 g. daily.

The urine passed during a good diuresis produced by amisometradine contains somewhat less chloride than sodium and therefore hypochloræmic alkalosis is not likely to develop, as it may after

mersalyl. If a larger series of patients should confirm that no clinically significant potassium loss is encountered after treatment with amisometradine, this would constitute an advantage over chlorothiazide, which causes potassium depletion in a considerable proportion of patients (Bayliss *et al.*, 1958; Slater and Nabarro, 1958).

Although mild nausea occurred in about one-quarter of our patients this could not be definitely attributed to the drug in any case. This is in contrast with aminometradine (mictine) which had to be withheld from 3 of another similar series of 18 patients with congestive cardiac failure because of nausea and vomiting (Platts and Hanley, 1956). However, amisometradine in doses of 800 to 2400 mg. did not seem to be quite so effective as aminometradine in doses of 400 to 800 mg. per day, which caused a "good" or "fair" diuresis in 16 out of 18 patients. Higher doses of amisometradine may produce better results but our limited experience does not suggest this.

Because of its delayed and uncertain action amisometradine is not the diuretic of choice for treatment of severe or recurrent congestive cardiac failure though it may be of use in restoring the response to mercurial diuretics. Its main use promises to be in the domiciliary treatment of mild congestive heart failure and in the maintenance of such patients after recovery.

Summary

Out of 17 patients with moderately severe congestive cardiac failure, 12 had a diuresis when treated with 800 to 2400 mg. of amisometradine daily. Six lost more than 0·5 kg. in weight daily.

Of 10 out-patients who had recovered from one or more attacks of heart failure, 2 remained well on reduced doses of mersalyl but 5 developed further attacks of heart failure.

Nausea occurred in 6 out of 23 patients but could not be definitely attributed to the amisometradine in any case. Eight out of 13 patients showed slight reduction in plasma potassium concentration during treatment: this produced no symptoms and no other toxic effects were encountered.

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References

Bayliss, R. I. S., Marrack, D., Pirkis, J., Rees, J. R., and Silva, J. F. (1958). *Lancet*, **1**, 120.
Belle, M. S. (1958). *Amer. Heart J.*, **55**, 114.
Jose, A. D., and Wood, P. (1958). *Brit. med. J.*, **1**, 9.
Platts, M. M., and Hanley, T. (1956). *Brit. med. J.*, **1**, 1078.
Sanderson, P. H. (1952). *Biochem. J.*, **52**, 502.
Settel, E. (1957). *Postgrad. Med.*, **21**, 186.
Slater, J. D. H., and Nabarro, J. D. N. (1958). *Lancet*, **1**, 124.